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## **Transmission of multidrug-resistant tuberculosis in a low-incidence setting, Switzerland, 2006 to 2012**

Somoskovi, A ; Helbling, P ; Deggim, V ; Hömke, R ; Ritter, C ; Böttger, E C

**Abstract:** The goal of the present study was to examine the transmission dynamics of multidrug-resistant tuberculosis (MDR-TB) in Switzerland. Between 2006 and 2012, a total of 49 MDR-TB cases were reported to the Swiss Federal Office of Public Health, 46 of which were of foreign origin. All 49 initial strains were evaluated by molecular epidemiologic methods at the Swiss National Reference Centre for Mycobacteria. In 43 strains, unique DNA fingerprint patterns were identified. Twelve strains were grouped into six clusters. Data from contact tracing suggest likely in-country transmission in four clusters, mostly among close contacts. In the remaining two clusters, no contact tracing data were available, but the identified genotypes were known to be prevalent in the countries of origin of the patients, suggesting the possibility that the infection was acquired there. While most MDR-TB cases are imported to Switzerland, at least four of the 49 MDR-TB cases were due to transmission within the country. The imported cases, however, did not lead to secondary cases outside the circles of close contacts. The results also indicate that prevention of MDR-TB transmission among immigrants may require closer monitoring.

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# Transmission of multidrug-resistant tuberculosis in a low-incidence setting, Switzerland, 2006 to 2012

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The goal of the present study was to examine the transmission dynamics of multidrug-resistant tuberculosis (MDR-TB) in Switzerland. Between 2006 and 2012, a total of 49 MDR-TB cases were reported to the Swiss Federal Office of Public Health, 46 of which were of foreign origin. All 49 initial strains were evaluated by molecular epidemiologic methods at the Swiss National Reference Centre for Mycobacteria. In 43 strains, unique DNA fingerprint patterns were identified. Twelve strains were grouped into six clusters. Data from contact tracing suggest likely in-country transmission in four clusters, mostly among close contacts. In the remaining two clusters, no contact tracing data were available, but the identified genotypes were known to be prevalent in the countries of origin of the patients, suggesting the possibility that the infection was acquired there. While most MDR-TB cases are imported to Switzerland, at least four of the 49 MDR-TB cases were due to transmission within the country. The imported cases, however, did not lead to secondary cases outside the circles of close contacts. The results also indicate that prevention of MDR-TB transmission among immigrants may require closer monitoring.

## Introduction

One of the most challenging concerns in tuberculosis control programmes, both in high and low-prevalence settings, is the emergence and transmission of multidrug-resistant tuberculosis (MDR-TB), by definition resistant at least to isoniazid and rifampicin [1]. The World Health Organization estimates 450,000 cases of MDR-TB to have occurred in 2012 worldwide, corresponding to 5.2% of all TB cases [2]. In Switzerland, the incidence of TB decreased steadily over many decades and seems to have reached a plateau in recent years at 7.0 per 100,000 population [3]. In the period 2005 to 2011, 71% of all TB cases in Switzerland were foreign-born. The proportion of culture-positive cases was 82.2% (3,093 of 3,763 cases) and 3,069 of the 3,093 culture-positive cases had susceptibility testing results, of which 47 (1.5%) had MDR-TB [3].

The goal of the present study was to analyse the transmission dynamics of MDR-TB in Switzerland by examining all MDR-TB strains identified in the country over a seven-year period using molecular methods and contact investigations in clustered cases.

## Methods

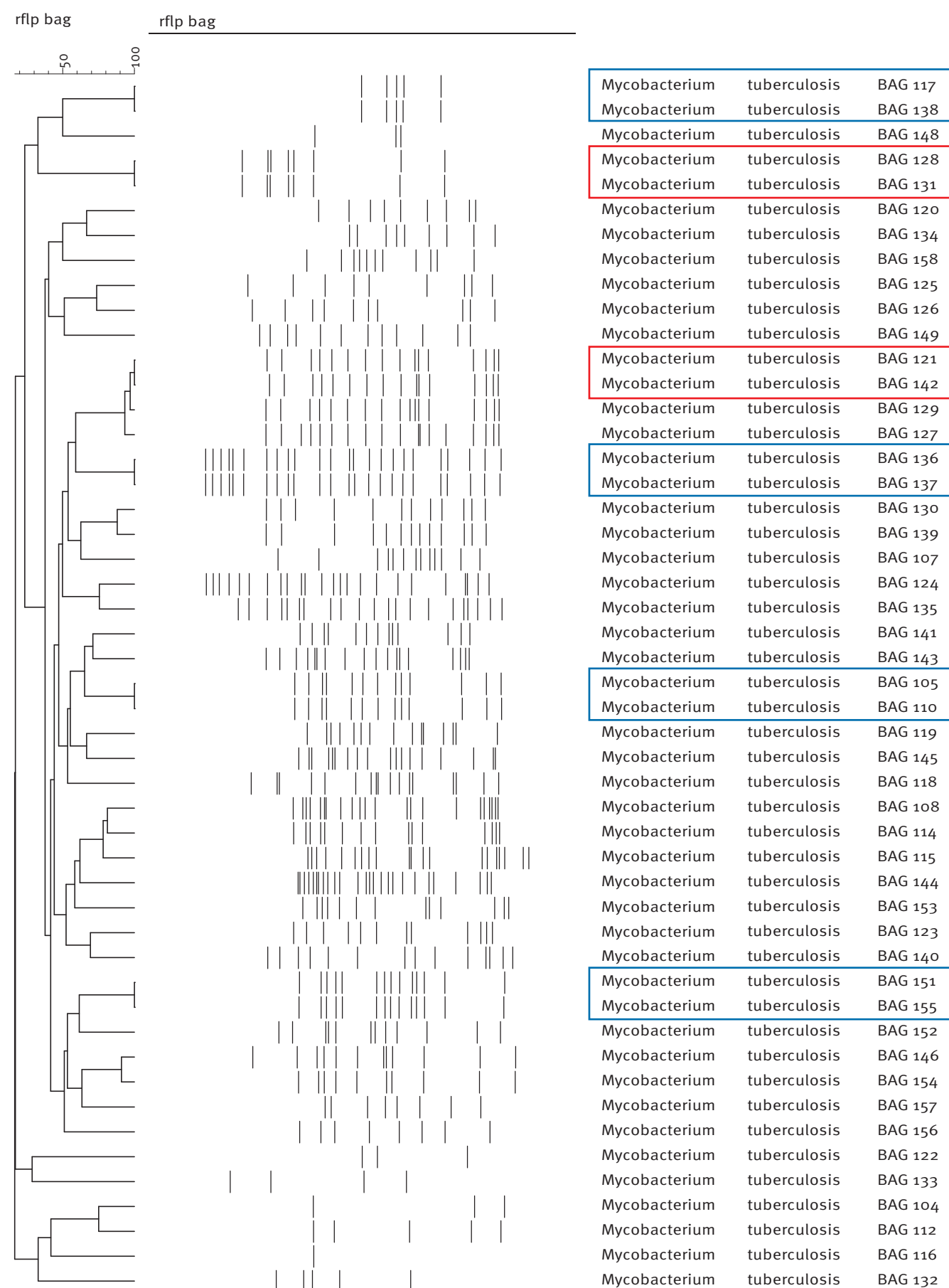
Since 1997, all laboratories in Switzerland have been submitting MDR-TB strains isolated in the country to the National Reference Centre for Mycobacteria (NZM). Cases were defined as MDR-TB when the isolate was resistant to at least isoniazid at 1.0 mg/mL and rifampicin at 1.0 mg/mL in the MGIT 960 system (Becton, Dickinson and Company) [4]. In the present study, we examined all initial MDR-TB isolates submitted to the NZM between January 2006 and December 2012. All strains (one strain per patient) were characterised by extensive conventional and molecular drug susceptibility testing as described earlier [4]. All isolates were also evaluated by IS6110 DNA restriction fragment length polymorphism (RFLP) fingerprinting, spoligotyping and 24-locus mycobacterial interspersed repetitive unit-variable number tandem repeat (MIRU-VNTR) as described previously [5-8]. Clusters were defined as groups of at least two patients with *Mycobacterium tuberculosis* strains showing identical IS6110 RFLP (same number of IS6110 bands at identical positions, position tolerance 1.2%), spoligotype and MIRU-VNTR patterns [7,8]. Baseline epidemiological data were obtained from the Swiss Federal Office of Public Health. Contact tracing was conducted by the local health authorities of the respective cantons. Results of the contact investigations were made available by the Lung Associations of Zurich and Bern ('Lunge Zürich' and 'Lungenliga Bern') acting on behalf of the respective health authorities.

## Results

Between 2006 and 2012, a total of 49 cases of MDR-TB were reported to the national surveillance system. None of the strains were extensively drug-resistant (XDR) isolates. Initial isolates of all these patients were submitted to the reference laboratory. Forty-six

## FIGURE

IS6110 fingerprint patterns of the 49 patients identified with multidrug-resistant tuberculosis and the 12 individuals in six clusters with identical fingerprints, Switzerland, 2006 and 2012 (n=49)



Blue: Clusters of patients with direct contact; red: clusters of patients for whom transmission in Switzerland is not probable.

patients were foreign-born and/or of foreign nationality. Of the three Swiss nationals, one had been living in Thailand and one was the teenage child of an MDR-TB patient born in sub-Saharan Africa, while no significant information could be identified on the exposure of the third individual.

Altogether, we identified 43 different DNA fingerprint patterns. Twelve of the 49 strains were grouped in six clusters with identical fingerprints, while 37 patients had individual fingerprints (Figure). Contact investigations of clustered patients confirmed epidemiological links in four clusters (Figure, highlighted in blue). First- and second-line drug susceptibility patterns were identical in all four clusters. All source cases of the four clusters were sputum smear-positive. In the remaining two clusters, the closest epidemiological link that could be confirmed was the geographical origin.

In the first cluster, the transmission event was identified among Tibetan immigrants and was from an adult to a child of pre-school age born in Switzerland. The source case was a friend of the family who regularly met and supervised the child. The primary contact investigation of the index case had not pointed to the child, who was diagnosed 10 months later and died of TB meningitis while under standard first-line treatment awaiting drug susceptibility testing results.

In the second cluster, transmission also occurred in Tibetan immigrants who were living together in Switzerland and had not met before their arrival to the country. Four weeks after the identification of the index case, asymptomatic active disease was detected radiologically in the contact during the contact investigation.

The third cluster was most likely the result of transmission between two immigrants from Turkey and Kosovo attending the same language school for several hours a day over many weeks. In this cluster, the contact tested tuberculin-negative eight weeks after the last exposure, but became symptomatic with pulmonary TB three years later.

The fourth cluster was due to transmission from a parent to their teenage child. The index patient had immigrated from Sub-Saharan Africa to Switzerland 14 years earlier. Pulmonary TB was identified in the asymptomatic child during the contact investigation.

The fifth molecular cluster consisted of two Ethiopians. One case was diagnosed with spinal TB one year before the second case was diagnosed with pulmonary TB and unknown sputum smear status. The contact investigation of the pulmonary case did not establish an epidemiological link and the investigation could not be re-opened for further investigations by the time the molecular epidemiological results became available.

The sixth cluster consisted of two patients from Ukraine and Estonia, diagnosed in 2007 and 2011: a tourist and

an asylum seeker, respectively, with different resistance profiles. Both patients could not be located any more for initiation of treatment. No additional data of contact tracing are available.

Molecular epidemiological testing of the fifth and sixth cluster (Figure, highlighted in red) showed the presence of strains with genotypes that were highly prevalent in the home countries of these patients: the ill-defined T family in Cluster 5, and the Beijing genotype in Cluster 6 [8,9].

Thus, at least four secondary cases (Clusters 1 to 4, highlighted in blue in Figure) were due to transmission within Switzerland during the examined period, corresponding to 8% of all MDR-TB cases in the country.

## Discussion

This report is providing molecular epidemiological insight into the transmission dynamics of MDR-TB in a low-incidence setting over a seven-year period. We have identified clustering in a quarter of the 49 MDR-TB strains that represent all MDR-TB cases reported nationwide in the period from 2006 to 2012. Transmission leading to secondary cases was confirmed by conventional contact tracing in four of the 49 cases. Transmission occurred mainly among persons living together or otherwise spending significant time together in a closed room on a regular basis over several weeks.

Comparable studies have been carried out in other resource-rich, low-incidence settings with similar population sizes and with a majority of TB cases occurring in immigrants (Table). A similar proportion of cases with recent transmission (7%; 2 of 29 MDR-TB cases) was found in Denmark over the period from 1992 to 2007 [10]. In a long-term and prospective follow-up of contacts exposed to MDR-TB patients in Victoria, Australia, the transmission rate was 5% (2 of 40 cases) in the period from 2002 to 2010 [11]. However, in a study in Galicia in the period from 1998 to 2004, with the vast majority of MDR-TB patients of Spanish origin, 53% of MDR-TB patients (30 of 57) were grouped in four clusters [12]. Unfortunately, drug susceptibility testing was not performed routinely on all clinical isolates in the latter study so that only about half of the MDR-TB cases estimated to have occurred were identified, thus possibly overestimating the proportion of clustering. Approximately half of the clustered cases could be attributed to recent transmission (two probable outbreaks, one of them nosocomial among patients and healthcare workers) [11]. In a German study representing an estimated 75% of all MDR strains occurring country-wide in 1995 to 2001, the rate of clustered MDR-TB cases was reported to be 49.4% (214 of 433 patients) [13]. Epidemiological links were established among 18.2% of the clustered patients (39 of 214), which corresponds to a proportion of cases with recent transmission of 5.8% (25 of 433). Taken together, these findings demonstrate that confirmed transmission of

**TABLE**

Proportion of multidrug-resistant tuberculosis cases with transmission to subsequent cases in different low-incidence settings

Reference	Geographical setting	Time period	Number of cases	Proportion of clustered cases	Proportion of confirmed transmissions with subsequent cases
[9]	Denmark	1992–2007	29	17%	7%
[10] <sup>a</sup>	Victoria, Australia	2002–2010	40	33%	5%
[11]	Galicia, Spain	1998–2004	57	53%	28%
[12]	Germany	1995–2001	433	49%	6%
This paper	Switzerland	2006–2012	49	25%	8%

<sup>a</sup> This study [10] calculated the proportion of confirmed transmission based on prospective and long-term follow-up of contacts, while the other studies calculated the proportion of multidrug-resistant tuberculosis cases attributable to recent transmission.

MDR-TB with subsequent progression to disease is not infrequent in settings with low incidence and with cases predominantly in immigrants.

MDR-TB may or may not differ from drug-susceptible TB in terms of transmissibility. At present, the effects of drug resistance on transmission of tuberculosis are only partly understood. On the one hand, delays in initiating adequate therapy may prolong infectiousness of a patient. On the other hand, drug resistance-associated mutations may lead to reduced fitness of the bacterium, which may decrease the chance of transmission [14–16]. As in other studies in small geographical areas with large proportions of patients from elsewhere, some of the contacts in our study may have remained in the area only for a limited period of time. This reduces the chances of the contact still being in the area, or in the country, when signs of active disease develop. Our study may thus underestimate the true extent of onward transmission particularly in population groups in which social contacts tend to be limited to fellow migrants. However, our results that all confirmed MDR-TB transmissions were identified in immigrants are in line with findings of a recent systematic review which found that transmission of TB from foreign-born patients does not have a significant influence on the TB situation in native-born populations in the European Union or European Economic Area [17]. A further limitation is that seven years of observation is a short time, seeing as cluster studies tend to underestimate clustering at the beginning and at the end of the study period, when source cases or secondary cases, respectively, are not included. The strength of our study is the completeness of the dataset, as all microbiologically confirmed MDR-TB cases of the country were assessed.

In conclusion, our findings show that considerable transmission of MDR-TB, leading to secondary cases, occurred in Switzerland between 2006 and 2012. However, our estimated transmission rate of 8% may be an underestimate of the true situation because the majority of MDR-TB cases were detected among

immigrants and their foreign contacts, who often leave the country before active disease develops. Our study also indicates that prevention of MDR-TB transmission among immigrants may warrant closer monitoring. Since treatment and management of each MDR-TB case may be complicated with uncertain outcomes, appropriate measures and structures must be in place so that cases can be handled adequately and timely, and transmission can be prevented.

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### Conflict of interest

None declared.

### Authors' contributions

Akos Somoskovi: study design, data and literature analysis, writing of manuscript;

Peter Helbling: data and literature analysis, writing of manuscript; Vanessa Deggim: data and literature analysis; Rico Hömke: molecular and conventional mycobacteriology testing, data analysis; Claudia Ritter: molecular and conventional mycobacteriology testing, data analysis; Erik C. Böttger: study design, data and literature analysis, writing of manuscript.

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